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10/626,037	07/23/2003	Warren J. Scherer	512-160	1255

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Ronald J. Baron, Esq.
HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
ROYDS, LESLIE A	
ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/626,037	SCHERER, WARREN J.	
	Examiner	Art Unit	
	Leslie A. Royds Draper	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 11 and 36 are presented for examination.

Applicant's Amendment filed December 28, 2010 has been received and entered into the present application.

Claims 11 and 36 remain pending and under examination. Claim 36 is amended.

Applicant's arguments, filed December 28, 2010, have been fully considered. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11 and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for topically applying an effective amount of the compound brimonidine tartrate per se for treating facial flushing associated with menopause-associated hot flashes in a human in need thereof by applying the compound locally to the facial skin of the human to be treated, does not reasonably provide enablement for topically applying an effective amount of a composition comprising an effective amount of a single component that reduces cutaneous facial flushing, wherein the single component consists of brimonidine tartrate, and a dermatologically acceptable carrier, for topical application locally to facial skin affected by facial flushing. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connect, to make the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision In re Wands, 8 USPQ 2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

The presently claimed invention is directed to a method of treating facial flushing associated with menopause-associated hot flashes in a human in need thereof, the method comprising topically administering a composition comprising an effective amount of a single component that reduces cutaneous facial flushing, wherein the single component consists of brimonidine tartrate, and a dermatologically acceptable carrier, locally to facial skin of the human, wherein the brimonidine tartrate acts locally to reduce cutaneous facial flushing. The claims further provide for the composition to further comprise an agent, or combination of agents, selected from the group consisting of antibacterial agents, anthelmintic agents, antioxidant agents, steroidal anti-inflammatory agents, non-steroidal anti-inflammatory agents, antiangiogenic agents, and derivatives of retinoic acid.

A fair reading of Applicant's instant claim 11 demonstrates the intent of the claim to provide for topical application of a composition that comprises brimonidine tartrate as the sole component of the composition that exerts an effect on the reduction of cutaneous facial flushing, to the exclusion of any other components and/or compounds that may have such an effect, to provide the claimed therapeutic

objective of treating facial flushing. However, the instant specification as originally filed lacks adequate guidance, direction or discussion to apprise the skilled artisan of the types of compositions of brimonidine tartrate in combination with a dermatologically acceptable carrier for topical application locally to facial skin that can be made for use in the context of the instantly claimed method, wherein the brimonidine tartrate is the sole component that functions to reduce cutaneous facial flushing as claimed. In the absence of such direction or guidance, the instant specification fails to provide adequate enabling disclosure to practice the full scope of the claimed subject matter.

Applicant discloses in the instant specification at p.5-6 that, "For the treatment of facial flushing in humans, one embodiment of the subject invention provides a (2-imidazolin-2-ylamino) quinoxaline derivative, such as brimonidine tartrate admixed with a dermatologically acceptable carrier which is then administered topically in accordance with the present invention to skin. Any suitable, conventional, dermatologically acceptable carrier may be employed. A carrier is dermatologically acceptable if it does not inhibit the effectiveness of the active compound(s) and it has substantially no long term or permanent detrimental effect on the skin to which it is administered. In various preferred embodiments, compositions of the subject invention are topically administered to facial skin.

The compositions encompassed by this invention include formulations for topical application to human skin. For topical application, one or more α_2 adrenergic receptor agonists, such as (2-imidazolin-2-ylamino) quinoxaline derivatives (a non-limiting example of which is brimonidine tartrate), may be formulated into any pharmaceutical form normally employed for such an application, in particular in the form of aqueous, aqueous/alcoholic or oily solutions, dispersions of lotion or serum type, aqueous anhydrous or lipophilic gels, emulsions of liquid or semi-liquid consistency of the milk type, obtained by dispersion of a fatty phase in an aqueous phase or conversely an aqueous phase in a fatty phase, or suspensions or emulsions of semi-solid or solid consistency of the cream or gel type, soaps or detergents, or alternatively microemulsions, microcapsules, microparticles, or vesicle dispersions of ionic and/or non-

ionic type. Among additional alternative means for topical application of compositions according to the subject invention are spray pumps, aerosol dispersions, impregnated cosmetic facial masks, and impregnated cosmetic facial cloths or sponges. These formulations may be produced by conventional techniques."

However, while such disclosure has been fully and carefully considered, it is noted that this same disclosure lacks a clear teaching, direction or guidance as to how to prepare topically applied compositions of the instant claims that comprise an effective amount of brimonidine tartrate and a dermatologically acceptable carrier, wherein brimonidine tartrate is the single component that functions to reduce cutaneous facial flushing, and the composition is suitable for topical application to the facial skin of the afflicted individual. Firstly, Applicant states that "any suitable, conventional, dermatologically acceptable carrier may be employed" and the carrier is considered dermatologically acceptable if it does not inhibit the effectiveness of the active compound (i.e., in the instant case, brimonidine tartrate) and does not have long term or permanent detrimental effects on the skin to which it is applied. However, this identified portion of the disclosure (see, p.5 et seq.) is non-specific as to those particular carriers that meet these requirements and also lack functionality in providing any degree of reduction in cutaneous facial flushing. Secondly, Applicant describes various formulations of the claimed composition that may be employed for the purpose of topical application directly to the facial skin of an afflicted subject, including "any pharmaceutical form normally employed for such an application", such as, e.g., aqueous, aqueous/alcoholic or oily solutions, suspensions or emulsions of semi-solid or solid consistency of the cream or gel type, impregnated cosmetic facial cloths or sponges, etc., and further teaches that the formulations may be produced by conventional techniques. However, once again, this identified portion of the disclosure (see, p.6 et seq.) is non-specific as to those particular types of topical formulations that meet these requirements and also lack functionality in providing any degree of reduction in cutaneous facial flushing.

Furthermore, the idea that the skilled artisan would have to look no further than "conventional" dermatologically acceptable carriers or "conventional" techniques to select an appropriate dermatologically acceptable carrier and/or topical formulation usable in the invention as instantly claimed that is devoid of activity in reducing cutaneous facial flushing resulting from menopause-associated hot flashes in a human afflicted by the same would not have been accepted on its face by one of ordinary skill in the art at the time of the invention. Prior art formulations for topical application to the skin, which include otherwise conventional "dermatologically acceptable carriers" are well known to provide cooling effects to the skin as a result of the inclusion of, e.g., water and/or alcoholic components. See, e.g., Simmons et al. (U.S. Patent No. 5,527,530), which describes alcohol/water based systems usable as after-shave lotions and suitable for application directly to the facial skin, which typically contain significant levels of alcohol, typically from about 50% to about 90% ethanol, which provides a skin tightening feeling and cooling effect as a result of their volatility and heat of vaporization (e.g., col.1, L.13-30; col.3, l.18-29). Lane et al. (U.S. Patent No. 4,661,476) describes a topical aqueous gel composition comprising about 75-99% water in combination with a polymeric component that provides a cooling sensation to the skin when applied directed to skin with an elevated temperature (col.2, l.1-29). Fleishmajer (U.S. Patent No. 3,674,027) describes dermatologically useful disposable open wet dressings that permit free evaporation of water that results in a cooling effect, as opposed to closed wet dressings that promote more maceration but less cooling (col.1, l.35-44; col.1, l.73-75), wherein the dressing is constructed from porous, smooth sheeting that can be directly applied to the skin (col.2, l.7-16). See also Wivell (U.S. Patent No. 5,525,344), which describes traditional cold cream formulations, named as such because of the cooling sensation generated when applied to the skin, which classically contained beeswax, mineral oil, water and borax (col.1 l.33-45). Luke (U.S. Patent No. 6,277,385) describes coolant compositions for topical application to the skin, such as lotions, gels, ointments, etc., which contain physiological coolants, such as menthol, which produces a cooling effect via direct action on nerve endings that are responsive to

hot and cold, or may also contain ethanol and other volatile alcohols that also provide coolant effects due primarily to the latent heat of evaporation from the skin (col.1, l.17-65).

The citations to these U.S. Patents is by no means intended to be an exhaustive list, but merely a representative selection from the multitude of prior art documenting that the state of the art at the time of the invention was replete with "conventional" dermatologically acceptable carriers and/or topical formulations that were known to provide cooling sensations to the skin and, accordingly, would be expected to contribute a cutaneous facial flushing reducing effect as a result of this cooling sensation, absent factual evidence to the contrary, were they used in the instant invention. As a result, it is plainly evident that the state of the art with regard to conventional, dermatologically acceptable and topically applied formulations clearly recognized the coolant properties of many conventional topical formulations for application to the skin, particularly those that contain water and/or alcoholic components. Thus, the selection of a dermatologically acceptable carrier and/or a particular type of topical formulation for application to the skin that does not concomitantly provide an effect on cutaneous facial flushing as a result of its ability to product a cooling sensation on the skin could not be made without needing to undertake undue experimentation to determine those carriers and/or topical formulations out of the myriad of those available in the art that would have no effect on reducing cutaneous facial flushing.

As is evident from Applicant's disclosure, the provision of cursory direction to select a "conventional" carrier and a topical formulation from an exemplary list that all appear to be aqueous (i.e., water) based and/or alcohol based, when it is clearly documented in the art (see U.S. Patents cited supra) that such carriers and formulations cool the skin (and, thus, would have been expected to provide a reduction in cutaneous facial flushing), fails to constitute adequate enabling guidance and/or direction to one of ordinary skill in the art at the time of the invention to select a dermatologically acceptable carrier and/or topical formulation that would not function to provide any reduction in cutaneous facial flushing when applied to the skin. In fact, it provides nothing more than an invitation to the skilled artisan to

execute hit or miss testing and experimentation to determine the metes and bounds of those carriers and/or formulations that would have had a benign effect (i.e., no effect, as required by the instant claims) on cutaneous facial flushing in a human subject suffering from menopause-associated hot flashes.

Notably, Applicant fails to provide any working embodiments or even prophetic embodiments describing a composition according to the instant claims, i.e., a composition comprising an effective amount of a single component that reduces cutaneous facial flushing, wherein the single component consists of brimonidine tartrate, and a dermatologically acceptable carrier, for application locally to the facial skin of a human in need of treatment of facial flushing associated with menopause related hot flashes. While the lack of a working and/or prophetic embodiment cannot be the sole factor in determining enablement, the absence of substantial evidence commensurate in scope with the breadth of the presently claimed subject matter, in light of the unpredictable nature of the art and the limited direction that Applicant has presented, provides additional weight to the present conclusion of insufficient enablement in consideration of the Wands factors as a whole.

The basis for the present rejection is not simply that experimentation would be required, since it is clear from the state of the prior art and Applicant's disclosure and remarks that experimentation in this particular art is not at all uncommon, but that the experimentation required in order to practice this aspect of the invention would be undue. Please reference In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976), which states, "The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." (emphasis added)

In view of the discussion of each of the preceding seven factors, the level of skill in the art is high and is at least that of a medical doctor or scientist with several years of experience in the art.

As the cited art and discussion of the above factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation or ability to make the full scope of the invention as instantly claimed, given the disclosure and supporting

examples provided in the present specification and the state of the art at the time of the invention. In order to actually achieve the claimed invention, it is clear from the discussion above that the skilled artisan could not rely upon Applicant's disclosure as required by 35 U.S.C. 112, first paragraph, and would have no alternative recourse but the impermissible burden of undue experimentation in order to practice the full scope of the embodiments presently claimed.

Conclusion

Rejection of claims 11 and 36 is proper.

No claims of the present application are allowed.

Applicant's amendment to instant claim 11 necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds Draper whose telephone number is (571)272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds Draper/
Primary Examiner, Art Unit 1614

March 11, 2011